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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/241,595	02/02/99	REIMANN J	9325-0008.30

022918
IOTA PI LAW GROUP
350 CAMBRIDGE AVENUE SUITE 250
P O BOX 60850
PALO ALTO CA 94306-0850

HM12/0920

EXAMINER	
BECKERLEG,A	
ART UNIT	**PAPER NUMBER**
1632	6

DATE MAILED: 09/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary	Application No. 09/241,595	Applicant(s) Reimann et al.
	Examiner Anne Marie S. Beckerleg	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-30 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-30 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4+5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-8, 10-13, 16-17, 20-21, 23, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to HBsAg particles containing an antigenic molecule and/or an immunostimulatory molecule. Claims 10, 16, and 23 further limit the immunostimulatory molecule to an oligonucleotide. The specification does not provide a written description for any molecules which are not proteins. The specification discloses immunostimulatory proteins such as cytokines or bacterial toxins and antigenic proteins or peptides such as the HIVenv/V3 peptide. However, it lacks guidance concerning the identity and chemical composition of antigenic molecules other than those composed of amino acids. In

regards to the recitation of immunostimulatory oligonucleotides, the specification does not describe whether the oligonucleotides comprise non-coding or protein coding sequence, or in the case of coding sequence, what the oligonucleotides encode.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). In the absence of any description of genes or nucleic acids encoding any immunostimulatory oligonucleotide or non-coding nucleic acid sequences which are immunostimulatory, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides which may be immunostimulatory, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. The nucleic acid itself is required. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Therefore, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for biologically active molecules which are not proteins. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification discloses HBsAg particles which non-covalently contain within the vesicle free space an antigenic protein and/or immunostimulatory molecule. The specification further discloses that HBsAg particles which contain a protein or peptide antigen can be used to vaccinate mammals against disease, particularly viral disease such as HIV, or that HBsAg particles which contain an immunostimulatory molecule such as a cytokine can be used to vaccinate against HBV, particularly in mammals which are typically non-responders to HBsAg particles alone, by stimulating or modulating immune responses in vivo. It is noted that claims directed to compositions comprising the HBsAg particles containing a biologically active molecule are included in this rejection in terms of "how to use" the molecules according to the disclosure of the specification.

The specification does not provide an enabling disclosure for making HBsAg particles which non-covalently contain inside the particles any biologically active protein. The specification discloses that the HBsAg particles are incubated with the protein, either the antigen, cytokine, or bacterial toxin, such that the protein is contained within the HBsAg particle. The particles themselves are described containing pores through which proteins can permeate the interior space, thus becoming "encapsulated". The specification's working examples utilize a soluble protein, OVA, and a soluble peptide, HIV/env/V3. Unlike soluble proteins which are typically hydrophilic

or neutral, proteins or peptides with hydrophobic regions would be attracted to the hydrophobic lipid/HBsAg layer, such that instead of entering the particle pores to be contained within the HBsAg layer, the skilled artisan might expect that proteins or peptides with hydrophobic regions would incorporate themselves into the particle layer. U.S. Patent No. 5,039,522, issued 8/13/91, (hereafter referred to as Neurath) describes just such a phenomenon. Neurath teaches that peptides with hydrophobic tails are absorbed by HBsAg particles (Neurath, column 3). The specification does not provide any guidance as to the physical and chemical conditions under which hydrophobic or insoluble proteins or peptides can be encapsulate into HBsAg particles. Thus, based on the nature of protein/protein and protein/lipid hydrophobic interactions, the teaching of Neurath et al. that peptides with hydrophobic tails are absorbed by HBsAg particles rather than encapsulated within, and the lack of guidance provided by the specification, the skilled artisan would not have predicted success in making HBsAg particles which encapsulate a hydrophobic or insoluble protein or peptide using the described methodology of incubating the two ingredients in aqueous solution.

The specification does not provide an enabling disclosure for stimulating immune responses against any soluble protein or peptide antigen by administering HBsAg particles which contain any amount of the antigen and/or any cytokine or bacterial toxin using any route of administration to any mammal. The specification discloses that antigenic peptides, cytokines, or bacterial toxins can be incorporated into HBsAg particles such that particles are capable of generating humoral and preferably cellular immune responses. In particular, the specification

teaches the generation of CTL responses against either the incorporated antigen or HBsAg itself. In another aspect of the invention, the specification discloses that the encapsulation into HBsAg particles of cytokines or bacterial toxins results in the induction of HBsAg immune responses in mice which normally fail to generate immune responses against empty HBsAg particles.

The specification's working examples demonstrate that HBsAg particles which encapsulate either OVA or HIV/env/V3 are capable of generating antigen specific CTL in Balb/C (responder) mice injected with the particles. It is noted that the specification does not indicate what route of administration was used in these examples. In terms of humoral immune responses, mice which received HBsAg-OVA generated low levels of OVA specific antibody which is less than that observed in the control mice which received OVA alone. The mice administered HBsAg-HIV/env/V3 apparently did not produce detectable levels of anti-HIV/env/V3 antibody. The working examples also demonstrate that HBsAg particles which encapsulate IL-12 or y-IFN are capable of generating an HBsAg specific CTL response in "non-responder" mice. Antibody responses are not reported. Finally, the specification reports but does not present data showing that non-responder mice administered HBsAg containing cholera toxin or staphylococcal enterotoxin generated both CTL and humoral responses.

The specification does not provide sufficient guidance for generating any kind of immune response, including a CTL response, using any antigen, any cytokine or bacterial toxin, and any dosage and route of administration. At the time of filing the prior art identifies several factors which significantly affect the generation of immune responses to an antigen which include,

genetics, dose or concentration of antigen, and route of antigen administration (Abbas et al. (1996) Nature, Vol. 383, 787-793, and Golding et al. (1994) Am. J. Trop. Med. Hyg., Vol. 50 (4), 33-40). The prior art teaches that the concentration of antigen significantly affects the development of cellular (Th1) versus humoral(Th2) immune responses such that low antigen concentrations preferentially induce Th1 type responses and high concentrations of antigen induce Th2 type responses (Abbas et al., *supra*). The antigens themselves have also been reported to affect the type of immune response generated. For example intracellular microorganisms such as *Salmonella, Leishmania, Malaria* and *Listeria* typically induce Th1 type responses, whereas schistosomiasis and *Nippostongylus* typically induce Th2 type responses. A further complicating factor is the genetic background of the infected mammal. The prior art contains numerous reports which demonstrate the Balb/C mice versus C57Bl/6 mice develop different responses to various pathogens. The nature and route of administration of the antigen is also of concern to the generation of a particular T helper phenotype. Golding et al. teaches that intravenous or intraperitoneal immunization leads to preferential induction of Th1 cells whereas subcutaneous or intramuscular immunization leads to Th2 cells which may be attributable to the participation of various antigen-presenting cells (Golding et al., *supra*). Thus, the art at the time of filing clearly teaches that a significant number of variables affect the generation of specific immune responses which render the generation of a particular type of immune response in any mammal unpredictable for any given antigen.

As discussed above, the specification's working examples demonstrate the generation of a CTL response to encapsulated OVA or HIV/env/V3 peptide. These are considered by the art to be strong antigens. However, the examples do not disclose the route of administration or disclose under which conditions the HBsAg were made. Figure 3 shows that the temperature at which the particles are incubated significantly affects the amount of peptide incorporated, which the largest amount incorporated at 56^{0}C. The specification does not provide guidance as to the dosage or concentrations of encapsulated antigen necessary to generate a CTL response or any other kind of immune response for weak antigens. In regards to the incorporation of cytokines or other immunostimulatory proteins in order to increase the immunogenicity of the particles, the specification's working examples only demonstrate increasing CTL responses to HBsAg particles using IL-12, y-IFN, or a bacterial entertoxin without disclosing the route of administration or the conditions under which the particles are formed. Of particular note, the working examples also demonstrate the unpredictability of identifying cytokines useful for increasing a particular type of immune response based on reported function. IL-2 has been associated in the literature with stimulating CTL responses. However, the specification's working examples show that HBsAg particles encapsulating IL-2 were ineffective in generating an HBsAg CTL response. Thus, in view of the art at the time of filing which teaches that a significant number of variables affect the generation of specific immune responses, the lack of specific guidance in the specification concerning routes of administration, conditions under which the HBsAg particles are formed, and cytokines and other immunostimulatory molecules useful for generating a particular type of

immune response to an antigen, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed in any host mammal using any HBsAg particle containing any antigen and/or immunostimulatory protein and any route of administration.

The specification does not provide an enabling disclosure for immunization against HBV or against diseases associated with antigen encapsulated by the HBsAg particles of the instant invention. The specification clearly discloses that the purpose of generating an immune response using the disclosed particles is for vaccination against disease, in particular HIV and HBV. However, the specification does not provide any guidance or experimental data which correlates the observed level of CTL response generated against HIV/env/V3 in mice administered HIV/env/V3 encapsulated in HBsAg particles, or against HBsAg in mice administered HBsAg particles encapsulating IL-12, y-IFN, cholera toxin or enterotoxin, with any effect on HIV or HBV infection. The art at the time of filing teaches that the strength and character of an immune response to a particular antigen or epitope significantly effects the ability of the host to successfully protect against or ameliorate disease or infection. For example, Yasutomi et al. teaches that immunization of rhesus monkeys with a live viral vector which encodes the SIV gag protein generates a non-protective CTL response, but fails to generate a humoral immune response despite the presence of MHC class II and antibody binding epitopes in the gag protein (Yasutomi et al. (1995) J. Virol., Vol. 69 (4), page 2279, abstract). In addition, Yasumtomi et al. teaches that while boosting vaccinated animals with a gag peptide/liposome complex significantly increases the anti-gag CTL response, it still did not provide increased protection against SIV

challenge (Yasumtomi et al., *supra*, abstract). As to immunization of humans against latent infectious agents such as HIV, Fox in a review of the "First National Conference on Human Retroviruses and Related Infections" summarizes the conference's central theme as, "no therapy has emerged as a sure winner in the campaign against HIV, not a preventive vaccine nor a therapeutic vaccine nor any of the immune-system-boosting treatments" (Fox (1994) Bio/Technology, 12, 128). Thus, in view of the art recognized unpredictability of vaccinating against HIV, the lack of correlation between the applicant's CTL data and any effect on HIV or HBV infection, and the breadth of the claims, the skilled artisan would not have predicted success in vaccinating any mammal against any disease by administering HbsAg particles encapsulating a disease antigen and/or immunostimulatory molecule.

The claims are free of the prior art of record for the following reasons. The prior art of record teaches the genetic modification of HbsAg to include antigenic epitopes including HIV/env/V3 such that the resulting particles contain HbsAg/HIV/env/V3 fusion proteins. The prior art of record also teaches the incorporation of antigenic peptide by chemical coupling or by hydrophobic absorption into the membranes formed by the HbsAg particles. However, since the claims recite that the antigen is "contained in" the HbsAg particles and the specification describes the HbsAg particles as "encapsulating" the antigen, thus excluding covalent or chemical attachment, the prior art of record does not teach or suggest the encapsulation of an antigen within an HbsAg particle such that the antigen is not covalently attached to the HbsAg proteins.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 8:30-6:00. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg

Karen M. Hauda

KAREN HAUDA
PRIMARY EXAMINER